REMARKS

Claims 1, 20-35 and 43-83 were pending and under consideration. Claims 43-70 have been re-numbered as Claims 56-83. Claims 1, 56-75, 79, 82 and 83 have been amended. Claims 76-78 have been withdrawn from consideration as drawn to a non-elected species (ApoA-I agonist-lipid complexes). Claims 20-35, 43-55 and 80-81 are canceled without prejudice. Thus, after entry of the instant amendment, Claims 1, 56-75, 79, 82-83 stand pending and under consideration. A version with markings to show changes made is attached at Exhibit A. For the Examiner's convenience, a clean copy of all pending claims is attached at Exhibit B.

I. THE AMENDMENT TO THE CLAIMS

Claim 1 has been amended to recite, in relevant part, an ApoA-I agonist compound comprising a 15 to 26-residue deleted peptide or deleted peptide analogue comprising formula (I). Support for amended Claim 1 can be found in the Claim 1 as originally filed and in the specification, for example, at page 50, line 11 to page 51, line 13.

Claims 58-65, 69, 73, 75, 79, 82 and 83 have been amended to correct dependency following re-numbering of the Claims. Claims 1, 56-75 and 79 have been amended to recite 'deleted peptide or deleted peptide analogues'. Support for amended Claims 1, 56-75 and 79 may be found in the claims as originally filed and in the specification, for example, at page 50, lines 11 to page 51, line 13.

Claims 82 and 83 have been amended to recite pharmaceutical compositions of ApoA-I agonists which are a lyophilized powder and a solution and to remove non-elected subject matter (ApoA-I agonist-lipid complexes). Support for amended Claims 82 and 83 can be found, for example, in page 85, line 5 to page 87, line 25.

As the amendments to the Claims are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

II. THE AMENDMENT TO THE SPECIFICATION

The specification has been amended to remove extraneous hand writing that was inadvertently present in the original specification on pages 65-69, (lines 1-36). Attached

herewith at Exhibit C are copies of pages 65-69, (lines 1-36), that have been redacted to remove said hand writing. The replacement pages 65-69, (lines 1-36) do not have any changes made to the text and therefore introduces no new matter. As said changes to the specification are fully supported by the parent application, 08/940,096, Applicants respectfully request entry of the amendment into the instant application.

III. RESTRICTION

The PTO has issued a further restriction in the pending matter. The PTO asserts that a restriction is necessary between ApoA-I peptide agonists and peptide-lipid complexes. Given that Applicants have received an action on the merits for ApoA-I agonists, the PTO asserts that ApoA agonists have been constructively elected. Accordingly, Claims 76 and 78 have been withdrawn from consideration.

Applicants reserve the right to pursue any unclaimed subject matter in one or more continuation, divisional or continuation-in-part applications.

IV. CLAIM REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Patent Office rejects Claims 56-75, 79-83 under 35 U.S.C. §112, second paragraph as allegedly being unclear as to the meaning of 'a deleted peptide or peptide analogue'. Claims 80 and 81 have been canceled rendering rejection of these claims moot.

Applicants submit that Claims 1, 56-64, 69-73, 75 and 79 are clear. However, merely to expedite passage of the claims to allowance, Claims 1, 56-75 and 79 have been amended to recite ApoA-I agonists that are deleted peptides or deleted peptide analogues. Applicants submit that amended Claims 1, 56-75 and 79 are clear and respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

V. CLAIM OBJECTIONS

The Patent Office objects to Claims 1, 65, 67-75, 79-83 for allegedly reading on non-elected subject matter (full-length ApoA-I agonists). Claims 80 and 81 have been canceled without prejudice rending the rejection of these claims moot.

Amended Claim 1 recites, in relevant part, an ApoA-I agonist compound comprising a 15 to 26-residue deleted peptide or deleted peptide analogue comprising formula (I).

Applicants respectfully submit that Claims 1, 65, 67-75, 79 and 82-83 do not read on non-elected subject matter and respectfully request that the objection be withdrawn.

VI. CLAIM REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 57 and 60-63 stand rejected as allegedly containing new matter as to 'two' helical turns. Claim 64 stands rejected as allegedly containing new matter in that Claim 64 recites 'residue 18 should not be deleted.' Claims 1, 56-75, 79-83 stand rejected for allegedly not being enabled.

A. NEW MATTER

The specification need not provide written description support in exactly the same words as are used in the claims. *Application of Luckach* 169 USPQ 795, 796 (CCPA 1971). It is enough that the specification conveys to those of skill in the art that the applicant had possession of the invention. *In re Wilder* 222 USPQ 369, 372 (Fed. Cir. 1984).

i. Two helical turns

The Patent Office rejects Claims 1, 57 and 60-63 as allegedly containing new matter, in that they recite deletion of two helical turns.

Applicants refer the Patent Office to the specification at page 50, lines 11 to 19. Therein is described peptides with 18 or even 15 residues. The specification describes ApoA-I agonists according to formula I that are, for example, 22 to 29 residues. (Page 51, lines 23 to 32). The specification also describes at page 51, lines 1 to 13 that an idealized α-helix contains 3.6 residues per turn, equivalent to 3 or 4 residues. The specification also describes that ApoA-I agonists may contain as few as 15 residues. It is apparent to one of skill in the art that deletion of six, seven or eight residues, for example, from a 29 residue ApoA-I agonist peptide would be the equivalent of deleting two helical turns, and still have 15 or more residues.

The specification teaches that the ApoA-I agonists are amphipathic α-helices that bind to lipids. (See Section VI, B, below). Deletion of residues from the ApoA-I agonists while maintaining α-helical structure is taught in the specification. The deletion of residues can be such that one or two helical turns are deleted. Thus, one of skill in the art would recognize that Applicants had possession of ApoA-I agonists with one or two helical turns deleted.

Applicants therefore respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

ii. **Deletion of X_{18}**

The Patent Office rejects Claim 64 as allegedly containing new matter, in that it recites the deletion of residue 18.

Amended Claim 64 recites the 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which residues 19, 20 and 22 are not deleted. Applicants therefore respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

B. ENABLEMENT

Claims 1, 56-75 and 79-83 stand rejected under 35 U.S.C. §112, first paragraph for allegedly not being enabled as to deleted peptides and deleted peptide analogues. Claims 80 and 81 have been canceled rendering rejection of these claims moot. Applicants respectfully traverse the rejection.

A claim is enabled if one of skill in the art, guided by Applicant's disclosure, can make and use the claimed invention without undue experimentation. *See, Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is not undue. *See, In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976).

Among the factors to be considered when determining whether the necessary experimentation is undue are the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See, In re Wands*, 8 U.S.P.Q.2d at 1404. In rejecting a claim for lack of enablement, the Examiner should cite any of these factors that are relevant, and specific technical reasons are always required. *See,* M.P.E.P. at §§ 2164.01(a) 2164.04; *In re Wands*, 8 U.S.P.Q.2d at 1404.

Applicants submit that Claims 1, 56-75, 79, 82 and 83 are fully enabled because the specification teaches one of skill in the art how to make and use the deleted peptide and deleted peptide analogues without undue experimentation.

The Patent Office asserts that the specification does not disclose a *core structure* required for the deletion analogues to maintain their biological activity. (Office Action dated, May 3, 2002, page 6). Applicants respectfully disagree.

Applicants respectfully point out that the peptides are not ApoA-I antagonists, but are agonists. (Office Action, dated May 3, 2002, page 6). Further, Applicants respectfully point out that the target molecule of the ApoA-I agonists is not ApoA-I, as indicated by the Patent Office. (*Id.*). Rather, that the full length, altered and deleted peptides and deleted peptide analogues are ApoA-I agonists that mimick the function of ApoA-I. The PTO's assertion that the ApoA-I agonists bind ApoA-I is erroneous. ApoA-I agonists, including deleted peptides, do not bind to ApoA-I for activity; but bind lipids, promote cholesterol efflux and activate LCAT.

The ApoA-I agonists form amphipathic α-helices in the presence of lipids, form pre β-like or HDL like complexes, activate LCAT, increase serum HDL concentration and promote cholesterol efflux. (Page 17, lines 18 to 27). The ApoA-I agonists activity is due to their ability to form amphipathic α-helices, for example, in the presence of lipids. An amphipathic α-helix is a secondary structure comprising individual amino acids that form a helix having a hydrophobic face and a hydrophilic face. As taught by the specification, any one amino acid can be substituted with another amino acid of a similar hydrophobicity while maintaining the overall amphipathic α-helix. Thus, the function of the ApoA-I agonists does not require the presence of any particular residue or any particular 'core structure' but rather the ability to form a secondary structure, namely an amphipathic α-helix in the presence of lipids.

The specification clearly teaches one of skill in the art how to make and use ApoA-I agonists and deletion analogues that form amphipathic α-helices in the presence of lipids without undue experimentation. Figures 1-5 provide Schiffer-Edmundson wheels of the amphipathic helices demonstrating the periodic arrangement of hydrophobic and hydrophilic residues. One face of the helix is occupied by hydrophobic residues and the other face occupied by hydrophilic residues, as explained in the specification, for example, at page 29, line 30 to page 30, line 15. Applicants submit that one of skill in the art, guided by the

specification, can delete at least one and up to eight residues and maintain the amphipathic α-helical structure illustrated in the Schiffer-Edmundson diagram.

The specification also teaches structural and physical properties of the deleted ApoA-I agonists. Such structural and/or physical properties of the ApoA-I agonists are degree of amphipathicity, overall hydrophobicity, mean hydrophobicity, hydrophobic and hydrophilic angles, hydrophobic moment, mean hydrophobic moment, and net charge of the α-helix. (Page 30, lines 16 to 23). For example, the ApoA-I agonists have a mean hydrophobic moment, $< \mu_H >$, from about 0.45 to about 0.65 and preferably from about 0.50 to about 0.60. The ApoA-I agonists have a mean hydrophobicity, $<H_o>$, from about -0.050 to about -0.070 and preferably from about -0.030 to about -0.055. The ApoA-I agonists have a mean hydrophobicity of the hydrophobic face, $< H_o^{pho} >$, from about 0.90 to about 1.20 and preferably from about 0.94 to about 1.10. The ApoA-I agonists have a pho angle from about 160° to about 220° and preferably from about 180° to about 200°. The specification teaches how to calculate these values at page 31, line 1 to page 33, line 2, and such calculations can easily be made by one of skill in the art. See, the specification at page 30, lines 31-32 and page 31, line 8, citing Eisenberg, 1984 *Ann. Rev. Biochem.* 53: 595-623 and Eisenberg, 1984 *J. Mol. Biol.* 179: 125-142. Thus, given the extensive teaching of the specification, one of skill in the art can use the mean hydrophobic moment, $< \mu_H >$, the mean hydrophobicity, $<H_o>$, the mean hydrophobicity of the hydrophobic face, $< H_o^{pho} >$, and the pho angle to make deleted ApoA-I agonists while maintaining the α-helical structure and ApoA-I agonist activity.

Furthermore, lipid binding activity of the ApoA-I agonists can be verified experimentally in a manner that does not require undue experiment. Indeed, such experimentation is routine to one of ordinary skill in the art. For example, when ApoA-I agonists are added to a turbid solution of lipids in water and mixed, the solution clarifies as the ApoA-I agonists bind to the lipids. Such an experiment is clearly within ordinary skill. The formation of amphipathic α-helices can also be determined, without undue experimentation, using the method of co-lyophilization. *See, e.g.,* U.S. Patent No. 6,287,590. Therein is described the verification of peptide/lipid binding by the mixture of peptides and lipids in miscible solvents, the peptides forming amphipathic α-helices in the presence of lipids. The peptide/lipid mixture is lyophilized and the lyophilized powder then reconstituted. Chromatographic spectra of the reconstituted mixture exhibits a single peak at

254 nm. Thus, one of skill in the art can use a simple and quick lipid binding experiment, without undue experimentation, to make deleted ApoA-I agonists.

Moreover, helicity can be determined quickly and simply by CD spectroscopy by one of skill in the art. The conditions under which ApoA-I agonist helicity is determined are described on page 94, line 8 to page 96, line 20. The exemplary peptide (SEQ ID NO: 146) contains significant helicity (86% helicity) at a concentration of 5 μM. (Page 95, lines 29 to 31). Those peptides that exhibited ≥38% LCAT activation exhibited ≥ 60% helical structure in the case of unblocked peptides containing 22 or more residues or blocked peptides containing 18 or fewer residues; ≥ 40% helicity in the case of unblocked peptides containing 18 or fewer amino acids. (Page 96, lines 3 to 20 and Table X). Use of CD spectroscopy is routine to one of skill in the art and the degree of experimentation needed to verify helicity of the ApoA-I agonists is not undue. See, specification at page 95, and references cited therein *e.g.*, Chen *et al.*, 1974, *Biochemistry* 13: 3350-3359, Provencher and Glockner, 1981, *Biochemistry* 20: 33-37 and Benyaminov *et al.*, 1993, *Anal. Biochem.* 214: 17-24. Thus, one of skill in the art could use peptide helicity as determined by CD spectroscopy to make deleted ApoA-I agonists.

Thus, Claims 1, 56-75, 79, 82 and 83 are fully enabled. The specification describes physical and structural properties of ApoA-I agonists important for activity. The specification describes the use of standard tools and techniques, such as Schiffer-Edmondson wheel and CD spectroscopy, which can be used without undue experimentation to make and use deleted ApoA-I agonists. Therefore, one of skill in the art, guided by the specification can make and use ApoA-I deleted peptides and deleted peptide analogues without undue experimentation. Applicants therefore respectfully request that the rejection be withdrawn.

VII. DOUBLE PATENTING

The Patent Office asserts that the Terminal Disclaimer over U.S. Patent Nos. 6,004,925, 6,037,323 and 6,265,377 is defective, allegedly because it lists six inventors. Applicants respectfully disagree.

A terminal disclaimer can overcome a double patenting rejection for the period the patent is commonly *owned* with the application or patent which forms the basis of the rejection. *See,* MPEP 706.02 (l)(3) and 804. The subject matter of the current application was invented by five inventors, Jean-Louis Dasseux, Renate Sekul, Klaus Büttner, Isabelle

Cornut and Günther Metz. The inventors then assigned their interests to six assignees. (Reel/Frame 9928/0452). The six assignees are: Jean-Louis Dasseux, Renate Sekul, Klaus Büttner, Isabelle Cornut, Günther Metz and Jean Dufourcq. The owners of U.S. Patent Nos. 6,004,925, 6,037,323 and 6,265,377 are Jean-Louis Dasseux, Renate Sekul, Klaus Büttner, Isabelle Cornut, Günther Metz and Jean Dufourcq. Thus, the pending application and U.S. Patents 6,004,925, 6,037,323 and 6,265,377 are commonly owned by the six assignees. Therefore, the Terminal Disclaimer is not defective. Applicants respectfully request that the rejection, if any, be withdrawn.

Claims 1, 57-76 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over copending Application No. 09/453,841. Applicants hereby request that the rejection be held in abeyance until an indication of patentable subject matter is given, at which point a Terminal Disclaimer may be filed.

VIII. RELATED PATENTS AND APPLICATIONS

For the PTO's convenience, Applicants identify applications related to the currently pending matter.

Applicants have three parent patents relating to the ApoA-I agonist compounds. These are U.S. Patent Nos. 6,004,925 (the '925 patent); 6,046,166 (the '166 patent) and 6,037,093 (the '093 patent). These patent families generally recite ApoA-I agonists of various formula I compositions, conservative substitutions, deletion analogues, multimers of formula II, III, IV and V and methods of treating dyslipidemia and septic shock.

A. U.S. Patent No. 6,004,925 and Related Patents and Applications

The '925 patent has six divisional applications and two continuations. Two of these divisional applications have issued as U.S. Patent Nos.: 6,376,464 and 6,329,341. The currently pending applications in this family are: U.S. Serial Nos.: 09/453,841; 09/453,840; 09/453,833; 09/453,826; 09/453,834 and 10/099,836.

U.S. Patent or Serial No.	Filing Date	Attorney Docket No.
6,004,925	September 29, 1997	9196-004-999
6,376,464	December 1, 1999	9196-013-999
6,329,341	December 1, 1999	9196-015-999

09/453,841	December 1, 1999	9196-010-999
09/453,840	December 1, 1999	9196-011-999
09/453,833	December 1, 1999	9196-012-999
09/453,826	December 1, 1999	9196-014-999
09/453,834	December 1, 1999	9196-016-999
10/099,836	March 15, 2002	9196-022-999

B. U.S. Patent No. 6,046,166 and Related Applications

The '166 patent has two continuations, U.S. Serial Nos. 09/465,718 and 10/099,574.

U.S. Patent or Serial No.	Filing Date	Attorney Docket No.
6,046,166	September 29, 1997	9196-005-999
09/465,718	December 17, 1999	9196-018-999
10/099,574	March 15, 2002	9196-021-999

C. U.S. Patent No. 6,037,323 and Related Patents and Applications

The '323 patent has two continuations, U.S. Serial Nos. 09/465,719 and 09/865,989. The '719 application has issued as U.S. Patent No. 6,265,377.

U.S. Patent or Serial No.	Filing Date	Attorney Docket No.
6,037,323	September 29, 1997	9196-006-999
6,265,377	December 17, 1999	9196-017-999
09/865,989	March 15, 2002	9196-019-999

CONCLUSION

Applicants submit that Claims 1, 56-75, 79, 82-83 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

To the extent the Examiner believes this matter is not in condition for allowance, Applicant's respectfully request an interview.

No fee is believed due with this Amendment. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-018-999). A copy of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date September 3, 2002

43,341

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EXHIBIT A

Claim Amendments: Version with Markings to Show Changes Made

1. (Amended) An ApoA-I agonist compound comprising:

(i) a 15 to [29] 26-residue deleted peptide or deleted peptide analogue comprising formula (I) which forms an amphipathic α-helix in the presence of lipids [and which comprises formula (I)] and in which one or two helical turns of the peptide or peptide analogue are optionally deleted :

Z_1 -X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7 - X_8 - X_9 - X_{10} - X_{11} - X_{12} - X_{13} - X_{14} - X_{15} - X_{16} - X_{17} - X_{18} - X_{19} - X_{20} - X_{21} - X_{22} -X_{23} -Z_2

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is Pro (P), Ala (A), Gly (G), Gln (Q), Asn (N), Asp (D) or D-Pro (p);

X_2 is an aliphatic residue;

X_3 is a Leu (L) or Phe (F);

X_4 is Glu (E)

X_5 is an aliphatic residue;

X_6 is Leu (L) or Phe (F);

X_7 is Glu (E) or Leu (L);

X_8 is Asn (N) or Gln (Q);

X_9 is Leu (L);

X_{10} is Leu (L), Trp (W) or Gly (G);

X_{11} is an acidic residue;

X_{12} is Arg (R);

X_{13} is Leu (L) or Gly (G);

X_{14} is Leu (L), Phe (F) or Gly (G);

X_{15} is Asp (D);

X_{16} is Ala (A);

X_{17} is Leu (L);

X_{18} is Asn (N) or Gln (Q);

X_{19} is a basic residue;

X_{20} is a basic residue;

X_{21} is Leu (L);

X_{22} is a basic residue;

X_{23} is absent or a basic residue;

Z_1 is R_2N- or RC(O)NR-;

Z_2 is -C (O) NRR or -C (O) OR;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one more bonds between residues 1-7 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each "-" between residues X_1 to X_{23} and between residues of the peptide to Z_2 independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic[; or

(ii) a 15 to 26-residue deleted peptide or peptide analogue according to formula (I) in which one or two helical turns of the peptide or peptide analogue are optionally deleted].

56. (Amended) The 15 to 26-residue deleted peptide or <u>deleted</u> peptide analogue of Claim 1, in which one helical turn is deleted.

57. (Amended) The 15 to 26-residue deleted peptide or <u>deleted</u> peptide analogue of Claim 1, in which three, four, six, seven or eight residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} , X_{18} , X_{19} , X_{20} , X_{21} and X_{22} are deleted.

58. (Amended) The 15 to 26-residue deleted peptide or <u>deleted</u> peptide analogue of Claim [44] <u>57</u>, in which 3 consecutive residues are deleted.

59. (Amended) The 15 to 26-residue deleted peptide or <u>deleted</u> peptide analogue of Claim [44] <u>57</u>, in which 4 consecutive residues are deleted.

60. (Amended) The 15 to 26-residue deleted peptide or <u>deleted</u> peptide analogue of Claim [44] <u>57</u>, in which two non-contiguous sets of 3 consecutive residues are deleted.

61. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [44] 57, in which two non-contiguous sets of 4 consecutive residues are deleted.

62. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [44] 57, in which one set of 3 consecutive residues and one set of 4 consecutive residues are deleted.

63. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [44] 57, in which 6, 7 or 8 consecutive residues are deleted.

64. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [44] 57, in which residues [18,]19, 20 and 22 are not deleted.

65. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [1] 57, in which residues 3, 6, 9 and 10 are not deleted.

66. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which X_{23} is absent.

67. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1 in which:
the "-" between residues designates -C (O) NH- ;
Z_1 is H_2N- ; and
Z_2 is -C (O) OH or a salt thereof.

68. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobic moment, $<\mu_H>$, is about 0.45 to about 0.65.

69. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [55] 68, in which the mean hydrophobic moment, $<\mu_H>$, is about 0.50 to about 0.60.

70. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobicity, $<H_o>$, is about -0.050 to about -0.070.

71. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobicity, $<H_o>$, is about -0.030 to about -0.055.

72. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.90 to about 1.20.

73. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [59] 72, in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.94 to about 1.10.

74. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the pho angle is about 160° to about 220°.

75. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim [61] 74, in which the pho angle is about 180° to about 200°.

79. (Amended) A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a deleted peptide or deleted peptide analogue according to Claim 1 or [44] 57.

82. (Amended) The pharmaceutical composition of Claim [80 or 81] 79 [in] which [the ApoA-I agonist compound-lipid complex] is [in the form of] a lyophilized powder.

83. (Amended) The pharmaceutical composition of Claim [80 or 81] 79 [in] which [the ApoA-I agonist compound-lipid complex] is [in the form of] a solution.

Exhibit B

Claim Amendments: Pending Claims After Entry of the Instant Amendment

1. (Amended) An ApoA-I agonist compound comprising:

(i) a 15 to 26-residue deleted peptide or deleted peptide analogue comprising formula (I) which forms an amphipathic α-helix in the presence of lipids and in which one or two helical turns of the peptide or peptide analogue are optionally deleted :

$$Z_1\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}X_8\text{-}X_9\text{-}X_{10}\text{-}X_{11}\text{-}X_{12}\text{-}X_{13}\text{-}X_{14}\text{-}X_{15}\text{-}X_{16}\text{-}X_{17}\text{-}X_{18}\text{-}X_{19}\text{-}X_{20}\text{-}X_{21}\text{-}X_{22}\text{-}X_{23}\text{-}Z_2$$

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is Pro (P), Ala (A), Gly (G), Gln (Q), Asn (N), Asp (D) or D-Pro (p);

X_2 is an aliphatic residue;

X_3 is a Leu (L) or Phe (F);

X_4 is Glu (E)

X_5 is an aliphatic residue;

X_6 is Leu (L) or Phe (F);

X_7 is Glu (E) or Leu (L);

X_8 is Asn (N) or Gln (Q);

X_9 is Leu (L);

X_{10} is Leu (L), Trp (W) or Gly (G);

X_{11} is an acidic residue;

X_{12} is Arg (R);

X_{13} is Leu (L) or Gly (G);

X_{14} is Leu (L), Phe (F) or Gly (G);

X_{15} is Asp (D);

X_{16} is Ala (A);

X_{17} is Leu (L);

X_{18} is Asn (N) or Gln (Q);

X_{19} is a basic residue;

X_{20} is a basic residue;

X_{21} is Leu (L);

X_{22} is a basic residue;

X_{23} is absent or a basic residue;

Z_1 is R_2N- or RC(O)NR-;

Z_2 is -C (O) NRR or -C (O) OR;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one more bonds between residues 1-7 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each "-" between residues X_1 to X_{23} and between residues of the peptide to Z_2 independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic.

56. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which one helical turn is deleted.

57. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which three, four, six, seven or eight residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} , X_{18} , X_{19} , X_{20}, X_{21} and X_{22} are deleted.

58. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which 3 consecutive residues are deleted.

59. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which 4 consecutive residues are deleted.

60. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which two non-contiguous sets of 3 consecutive residues are deleted.

61. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which two non-contiguous sets of 4 consecutive residues are deleted.

62. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which one set of 3 consecutive residues and one set of 4 consecutive residues are deleted.

63. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which 6, 7 or 8 consecutive residues are deleted.

64. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which residues 19, 20 and 22 are not deleted.

65. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 57, in which residues 3, 6, 9 and 10 are not deleted.

66. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which X_{23} is absent.

67. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1 in which:
the "-" between residues designates -C (O) NH- ;
Z_1 is H_2N- ; and
Z_2 is -C (O) OH or a salt thereof.

68. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobic moment, $<\mu_H>$, is about 0.45 to about 0.65.

69. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 68, in which the mean hydrophobic moment, $<\mu_H>$, is about 0.50 to about 0.60.

70. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobicity, $<H_o>$, is about -0.050 to about -0.070.

71. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobicity, $<H_o>$, is about -0.030 to about -0.055.

72. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.90 to about 1.20.

73. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 72, in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.94 to about 1.10.

74. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 1, in which the pho angle is about 160° to about 220°.

75. (Amended) The 15 to 26-residue deleted peptide or deleted peptide analogue of Claim 74, in which the pho angle is about 180° to about 200°.

79. (Amended) A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a deleted peptide or deleted peptide analogue according to Claim 1 or 57.

82. (Amended) The pharmaceutical composition of Claim 79 which is a lyophilized powder.

83. (Amended) The pharmaceutical composition of Claim 79 which is a solution.

EXHIBIT C

Specification Amendment: Specification After Entry of the Instant Amendment

peptides exhibiting 50%, 60%, 70%, 80% or even 90% or more being particularly preferred.

5.1.2. PREFERRED EMBODIMENTS

The ApoA-I agonists of the invention can be further defined by way of preferred embodiments.

In one preferred embodiment, the ApoA-I agonists are 22 amino acid residue peptides according to structure (I), or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof.

In another preferred embodiment, the ApoA-I agonists are 22 amino acid residue peptides according to structure (I), or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, in which:

X_1 is Pro (P), Gly (G), Ala (A), Asn (N) or D-Pro (p);

X_2 is Ala (A), Val (V) or Leu (L);

X_5 is Leu (L);

X_6 is Phe (F);

X_{11} is Glu (E);

X_{19} is Lys (K);

X_{20} is Lys (K); and/or

X_{22} is Lys (K), and each of X_3, X_4, X_7, X_8, X_9, X_{10}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18} and X_{21} are as previously defined for structure (I).

Particularly preferred ApoA-I agonists according to this aspect of the invention are those in which X_2 is Val (V); and/or X_{18} is Gln (Q).

In still another preferred embodiment, the ApoA-I agonists are 22 amino acid residue peptides according to structure (I), or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, in which one of X_{10}, X_{13} or X_{14} is Gly (G) and the others of X_{10}, X_{13} and X_{14} are other than Gly (G). When X_{14} is Gly (G), X_7 is preferably Glu (E).

Particularly preferred ApoA-I agonists according to this aspect of the invention are peptides selected from the group consisting of:

peptide **148**: PVLELFENLLERLGDALQKKLK (SEQ ID NO:148);
peptide **151**: PVLELFENLGERLLDALQKKLK (SEQ ID NO:151);
peptide **154**: PVLELFENLLERGLDALQKKLK (SEQ ID NO:154);
and the N-terminal acylated and/or C-terminal amidated or esterified forms thereof.

Embodiments containing internal glycine residues can be readily synthesized in high yield by way of segment condensation, thereby providing significant advantages for large-scale production. Segment condensation, i.e., the joining together of small constituent peptide chains to form a larger peptide chain, has been used to prepare many biologically active peptides, including 44-amino acid residue mimics of ApoA-I (see, e.g., Nakagawa et al., 1985, J. Am Chem. Soc. 107:7087-7083; Nokihara et al., 1989, Peptides 1988:166-168; Kneib-Cordonnier et al., 1990, Int. J. Pept. Protein Res. 35:527-538), and is considered to be the most cost-effective method for high-yield bulk synthesis of the core peptides of the invention.

Advantages of synthesis via segment condensation include the ability to condense pre-formed segments in the solution phase and the ease of purification of the final product. Drawbacks of the method include low coupling efficiency and yield at the condensation step and low solubility of certain peptide sequences.

The coupling efficiency of the condensation step can be significantly increased by increasing the coupling time. Typically, increasing the coupling time results in increased racemezation of the product (Sieber et al., 1970, Helv. Chim. Acta 53:2135-2150). However, since glycine lacks a chiral center it does not undergo racemezation (proline residues, due to steric hindrance, also undergo little or no racemezation at long coupling times). Thus, embodiments containing internal glycine residues can be synthesized in bulk in high yield via segment condensation by synthesizing constituent segments which take advantage of the fact that glycine residues do not undergo racemezation. Thus,

embodiments containing internal glycine residues provide significant synthetic advantages for large-scale bulk preparation.

In still another preferred embodiment, the ApoA-I agonists are 22-amino acid residue peptides according to structure (I), or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, in which each of X_{10}, X_{13} and X_{14} is other than Gly (G).

In still another preferred embodiment, the ApoA-I agonists are altered or mutated forms of the peptides according to structure (I), or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, in which:

X_4 is other than Asp (D);
X_5 is other than Phe (F);
X_6 is other than Trp (W);
X_7 is other than Leu (L) or Asp (D);
X_9 is other than Gly (G) or Trp (W);
X_{12} is other than Lys (K);
X_{13} is other than Trp (W);
X_{14} is other than Trp (W);
X_{15} is other than Glu (E);
X_{16} is other than Trp (W) or Leu (L); and/or
X_{17} is other than Trp (W).

In still another preferred embodiment, the ApoA-I agonists are 22 amino acid residue peptides according to structure (I), or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, in which when X_7 is Leu (L), X_{10} is Trp (W), X_1 is other than Gly (G) and/or X_{14} is other than Gly (G). A particularly preferred peptide according to this aspect of the invention is peptide **155** (PVLELFLNLWERLLDALQKKLK; SEQ ID NO:155).

In another preferred embodiment, the ApoA-I agonists are 22-amino acid-residue peptides, or the N-terminal acylated and/or C-terminal amidated or esterified forms thereof, in which at least one of X_{19}, X_{20} or X_{22} is other than Orn. More preferably, at least two of X_{19}, X_{20} and X_{22} are

other than Orn. Most preferably, each of X_{19}, X_{20} and X_{22} is other than Orn.

In still another preferred embodiment, the ApoA-I agonists are selected from the group of peptides set forth below:

peptide **144**: pVLELFENLLERLLDALQKKLK (SEQ ID NO:144);
peptide **145**: GVLELFENLLERLLDALQKKLK (SEQ ID NO:145);
peptide **146**: PVLELFENLLERLLDALQKKLK (SEQ ID NO:146);
peptide **147**: PVLELFENLLERLFDALQKKLK (SEQ ID NO:147);
peptide **148**: PVLELFENLLERLGDALQKKLK (SEQ ID NO:148);
peptide **149**: PVLELFENLWERLLDALQKKLK (SEQ ID NO:149);
peptide **150**: PLLELFENLLERLLDALQKKLK (SEQ ID NO:150);
peptide **151**: PVLELFENLGERLLDALQKKLK (SEQ ID NO:151);
peptide **152**: PVFELFENLLERLLDALQKKLK (SEQ ID NO:152);
peptide **153**: AVLELFENLLERLLDALQKKLK (SEQ ID NO:153);
peptide **154**: PVLELFENLLERGLDALQKKLK (SEQ ID NO:154);
peptide **155**: PVLELFLNLWERLLDALQKKLK (SEQ ID NO:155);
peptide **186**: PVLELFEQLLERLLDALQKKLK (SEQ ID NO:186);
peptide **187**: PVLELFENLLERLLDALNKKLK (SEQ ID NO:187);
peptide **188**: PVLELFENLLDRLLDALQKKLK (SEQ ID NO:188);
peptide **189**: DVLELFENLLERLLDALQKKLK (SEQ ID NO:189);

and the N-terminal acylated and/or N-terminal amidated or esterified forms thereof.

In still another preferred embodiment, the ApoA-I agonists are selected from the group of peptides set forth below:

peptide **144**: pVLELFENLLERLLDALQKKLK (SEQ ID NO:144);
peptide **145**: GVLELFENLLERLLDALQKKLK (SEQ ID NO:145);
peptide **146**: PVLELFENLLERLLDALQKKLK (SEQ ID NO:146);
peptide **147**: PVLELFENLLERLFDALQKKLK (SEQ ID NO:147);
peptide **148**: PVLELFENLLERLGDALQKKLK (SEQ ID NO:148);
peptide **149**: PVLELFENLWERLLDALQKKLK (SEQ ID NO:149);
peptide **150**: PLLELFENLLERLLDALQKKLK (SEQ ID NO:150);
peptide **151**: PVLELFENLGERLLDALQKKLK (SEQ ID NO:151);
peptide **152**: PVFELFENLLERLLDALQKKLK (SEQ ID NO:152);
peptide **153**: AVLELFENLLERLLDALQKKLK (SEQ ID NO:153);

peptide **154**: PVLELFENLLERGLDALQKKLK (SEQ ID NO:154);
peptide **155**: PVLELFLNLWERLLDALQKKLK (SEQ ID NO:155);
and the N-terminal acylated and/or C-terminal amidated or esterified forms thereof.

In yet another preferred embodiment, the ApoA-I agonists are multimeric forms according to structures II, III and/or IV in which each HH is independently a peptide according to structure (I) or an N-terminal acylated and/or C-terminal amidated or esterified form thereof, or any of the preferred peptides according to structure (I) described herein.

In yet another preferred embodiment, the core peptides that compose the ApoA-I agonists are not any of the following peptides:

peptide **75**: PVLDEFREKLNEELEALKQKLK (SEQ ID NO:75);
peptide **94**: PVLDEFREKLNEALEALKQKLK (SEQ ID NO:94);
peptide **109**: PVLDEFREKLNERLEALKQKLK (SEQ ID NO:109);
peptide **237**: LDDLLQKWAEAFNQLLKK (SEQ ID NO:237);
peptide **238**: EWLKAFYEKVLEKLKELF* (SEQ ID NO:238);
peptide **241**: DWFKAFYDKVFEKFKEFF (SEQ ID NO:241);
peptide **242**: GIKKFLGSIWKFIKAFVG (SEQ ID NO:242);
peptide **243**: DWFKAFYDKVAEKFKEAF (SEQ ID NO:243);
peptide **244**: DWLKAFYDKVAEKLKEAF (SEQ ID NO:244);
peptide **245**: DWLKAFYDKVFEKFKEFF (SEQ ID NO:245);
peptide **246**: EWLEAFYKKVLEKLKELF (SEQ ID NO:246);
peptide **247**: DWFKAFYDKFFEKFKEFF (SEQ ID NO:247);
peptide **248**: EWLKAFYEKVLEKLKELF (SEQ ID NO:248);
peptide **249**: EWLKAEYEKVEEKLKELF* (SEQ ID NO:249);
peptide **250**: EWLKAEYEKVLEKLKELF* (SEQ ID NO:250); and
peptide **251**: EWLKAFYKKVLEKLKELF* (SEQ ID NO:251).

In a final preferred embodiment, the ApoA-I agonists are not any of the peptides listed in TABLE X (Section 8.3, infra) which exhibit an LCAT activation activity of less than 38% as compared with native human ApoA-I.